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CLINICAL REVIEW

To ED or not to ED – Is erectile dysfunction in obstructive sleep apnea related to endothelial dysfunction?

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SUMMARY

Both obstructive sleep apnea (OSA) and erectile dysfunction (ErectD) are highly prevalent and largely under diagnosed medical conditions. These disorders often co-exist, with about half of the male OSA population having ErectD and vice versa. OSA is strongly associated with an increased risk of cardiovascular mortality while ErectD has been proposed as a phenotypic marker of cardiovascular disease. This implies that the two conditions may be linked by a common pathophysiological mechanism. In this review we provide evidence supporting the hypothesis that endothelial dysfunction (EndoD) may be the common pathophysiological mechanism linking OSA with both ErectD and cardiovascular complications. EndoD is one of the earliest markers of cardiovascular disease and substantial evidence suggests that OSA independently causes EndoD. There is also strong evidence that causally links EndoD with organic ErectD. Further research should be directed at determining the value of simultaneously assessing both ErectD and OSA in patients presenting with symptoms of either condition. In both ErectD and OSA clinics, identifying both conditions could improve overall cardiovascular risk stratification whilst treatment of OSA could reduce both ErectD and cardiovascular risk.

Introduction

Erectile dysfunction (ErectD) is the inability to obtain and maintain a penile erection sufficient for penetration [1] and is both highly prevalent and inadequately treated. In 1995, 150 million men reported some degree of ErectD and this prevalence is predicted to increase to 322 million by 2025 [2]. ErectD is now recognized as an important sentinel event for cardiovascular disease (CVD) which requires more aggressive CVD risk reduction strategies [3,4]. It has been proposed that the link between ErectD and CVD is endothelial dysfunction (EndoD) which may manifest early in the smallest vessels of the body. EndoD is the earliest sign of vascular damage and has been shown to have prognostic value in regards to the likelihood of future cardiovascular events [5,6].

Untreated obstructive sleep apnea (OSA) is independently associated with increased all-cause mortality [7–9], cardiovascular mortality [8–10] and cardiovascular events [10,11]. The cardiometabolic consequences of OSA such as hypertension [12], insulin resistance [13] and diabetes [14,15] are all well recognized. The link between OSA and obesity, particularly visceral abdominal fat which is one of the central components of the metabolic syndrome, is also well known [16,17]. OSA is also associated with ErectD, low libido and biochemical androgen deficiency; however these relationships are not commonly assessed and are therefore far less recognized. This is despite cross-sectional studies showing that ErectD occurs in half of all men with OSA independent of obesity [18,19] and that OSA treatment with continuous positive airway pressure (CPAP) improves ErectD [20] and possibly reproductive hormones [21,22]. OSA is also strongly associated with EndoD, with evidence of a causal relationship through a number of mechanistic pathways (Fig. 1) [23,24]. Thus the resulting EndoD in

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Abbreviations

ADMA	asymmetric dimethylarginine
AHI	apnea hypopnea index
CVD	cardiovascular disease
ErectD	erectile dysfunction
EndoD	endothelial dysfunction
FMD	flow mediated dilatation
IIEF	international index of erectile function
NPT	nocturnal penile tumescence monitoring
OSA	obstructive sleep apnea
PDE5	phosphodiesterase type 5
PSG	polysomnography
REM	rapid eye movement

OSA may explain the increased rate of ErectD in this population. Consequently the independent association between OSA [25] and ErectD [26] with worsened cardiovascular outcome may be through EndoD. Men with both OSA and ErectD are likely to have markedly impaired endothelial function and thus be at substantially increased CVD risk. This review will examine the evidence suggesting that OSA causes ErectD by promoting EndoD (Fig. 1). Previous reviews have examined the relationship between testosterone and sexual function with obesity [27] and sleep [28], and we have previously reviewed the relationship between testosterone, obesity and OSA [29] hence this review will not examine hormonal relationships.

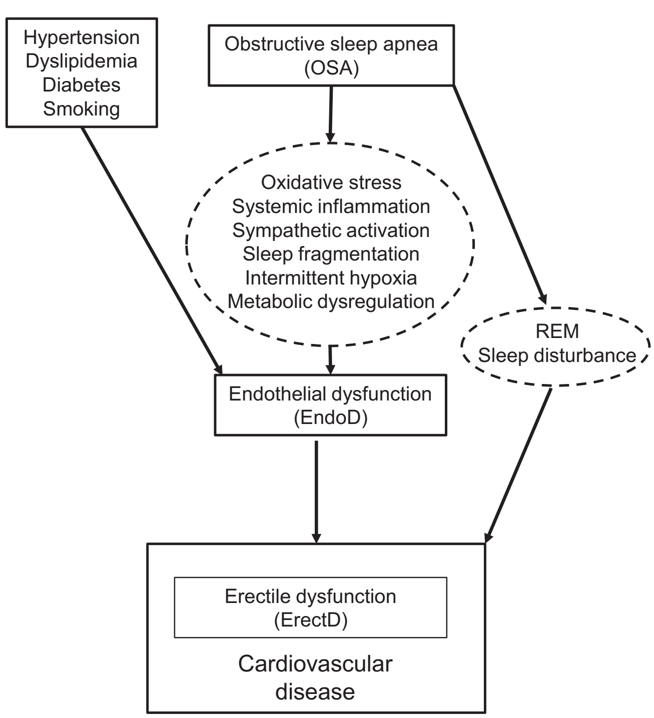

Fig. 1. Different causes of endothelial dysfunction and in turn erectile dysfunction which is a silent early marker of cardiovascular disease. The plausible mechanisms in which OSA may directly cause both endothelial dysfunction and erectile dysfunction are shown in the circles. REM = rapid eye movement.

ErectD – measurement and prevalence

ErectD is the most common cause of sexual dissatisfaction, surpassing loss of sexual desire (libido) and ejaculatory dysfunction. ErectD is highly prevalent, with approximately 20% of men in Australia [30,31] reporting the condition. Rates are similar in North and South America [32–36] with 10–17% overall, increasing to 50–60% in older age groups. The underlying cause of ErectD can be organic, psychogenic or a combination of the two. Organic ErectD represents 60–80% of all cases and is caused by underlying chronic diseases such as Parkinson's disease, stroke, diabetes, obesity, hypertension and atherosclerosis [1,37]. The remaining cases are due to psychogenic causes including performance anxiety, lack of sexual excitement, depression and schizophrenia [1]. Traditionally, the differentiation between psychogenic and organic was evaluated by the measurement of sleep related erections normally associated with rapid eye movement (REM) sleep using nocturnal penile tumescence monitoring (NPT). Patients with psychogenic ErectD typically have preserved erections during REM sleep. However because more recently both forms of the condition are generally treated similarly, NPT testing is not always clinically necessary. The international index of erectile function (IIEF) questionnaire is currently the gold standard assessment tool for ErectD [38]. There are, however, numerous other validated ErectD measurements that have been used in the research setting [39–46].

ErectD and CVD

Most of the traditional risk factors for CVD including older age, obesity, cigarette smoking, diabetes, hyperlipidemia and hypertension have been causally associated with ErectD [4,47] (Fig. 1). Indeed, two large prospective longitudinal studies have shown that age, smoking and being overweight are associated with the subsequent development of ErectD after 8–10 [36] and 25 [48] years of follow-up. However the presence of ErectD is increasingly being recognized as an early warning sign of CVD prior to developing overt cardiovascular symptoms [4]. In support of this, prospective studies [49–52] and a retrospective study [53] suggest that ErectD can predict subsequent CVD. Additionally, a recent large population-based longitudinal study found that self-reported ErectD was associated with both cardiovasular-mortality and all-cause mortality after adjusting for known risk factors [54]. The presence of ErectD has been shown to be comparable to smoking or a familial history of myocardial infarct as a marker for developing cardiovascular disease [49,53,54]. Therefore, ErectD may have important prognostic value for CVD development which suggests that those men who present with ErectD should be screened for CVD and other associated risk factors [49].

EndoD – definition, measurement and role in CVD

The vascular endothelium is critical for many functions including the maintenance of vascular tone, platelet activity, vessel wall inflammation, smooth muscle proliferation and cellular adhesion. The healthy endothelium secretes nitric oxide, which combats atherosclerosis through local vasodilation as well as inhibition of platelet aggregation, monocyte adhesion and vascular smooth muscle proliferation. Clinically EndoD is assessed by measuring the vasodilator response to an increase in blood flow or to infusion of a vasodilator (e.g., acetylcholine) [55]. EndoD is well known to be exacerbated by traditional cardiovascular risk factors including smoking, age and dyslipidemia and has been implicated

Table 1
Population studies investigating the association between ErectD and OSA.

First author	*N*	Age (y)	ErectD measure	OSA measure	Results
Andersen (2010) [35]	467	Range: 20–80	MMAS single question	PSG	Odds ratio 2.75** of having OSA (AHI > 15) if have ErectD compared to no OSA (AHI < 5).
Hanak (2007) [75]	827	64 (51, 90)	BMSFI	Snoring questionnaire	Heavy snorers twice as likely to have lower sexual satisfaction compared to mild/non-snorers, after adjustment for potential confounders. No association between degree of snoring and erectile function.
Schiavi (1991) [118]	70	Range: 45–75	NPT & psychosexual interview	Partial PSG (no SaO_2 or respiratory effort)	No correlation between sleep disordered breathing parameters and NPT/sexual behavior parameters once age was accounted for.
Heruti (2005) [74]	3363	36 ± 7	IIEF-5	Sleep quality questionnaire	Correlation between IIEF-5 and SQ ($r = -029$**). SQ not specific to sleep apnea.

Data are mean ± standard deviation or median (25th, 75th percentiles) unless otherwise stated, $^{**}p < 0.01$. AHI = apnea hypopnea index, BMSFI = brief male sexual functioning inventory, ErectD = erectile dysfunction, IIEF-5 = 5-item international index of erectile function, MMAS = Massachusetts male aging study, NPT = nocturnal penile tumescence, PSG = polysomnography, SaO_2 = blood oxygen saturation, SQ = sleep quality.

as one of the earliest detectable abnormalities initiating atherosclerosis and the development of CVD.

EndoD as a cause for ErectD

It has been demonstrated that EndoD is a root cause of ErectD. EndoD therefore represents the pathophysiological link between ErectD and this increased cardiovascular risk [56] (Fig. 1). This is because EndoD impairs the endothelial cells ability to release nitric oxide which can cause the inability of the smooth muscle to relax. This in turn results in inadequate endothelial vasodilatation and lack of blood flow to the corpora cavernosa can lead to ErectD. This has been demonstrated in vitro with both neurogenic and endothelium-dependant relaxation being impaired in isolated corpus cavernosum strips from patients with ErectD [57]. Since the diameter of the penile artery is smaller than that of the coronary artery, it has been hypothesized that generalized atheromatous disease which arises from EndoD, manifests as ErectD first.

Penile endothelial function, measured by the change in blood flow through the penis as determined by plethysmography, has been shown to be impaired in men with ErectD [58] . However peripheral endothelial function, measured at the forearm, has been studied more commonly and these measures are more generalizable to clinical populations. Studies have repeatedly found EndoD, as measured by flow mediated dilatation (FMD) in the brachial artery, to be impaired in ErectD patients compared to healthy controls [59–61]. In contrast EndoD using a different method, venous occlusion plethysmography, found no difference between patients and controls [58]. This discrepancy may be because FMD measures vasodilatation of the larger brachial artery whereas venous plethysmography measures this in the microvasculature. Furthermore asymmetric dimethylarginine (ADMA) levels, which interfere with the production of nitric oxide, are elevated in men with ErectD compared to healthy men or men with coronary artery disease and are predictive of ErectD severity [62]. Similar results have been reported in men with other conditions such as metabolic syndrome [63]. Additionally endothelium-independent vasodilatation has been shown to be impaired in men with ErectD and vascular risk factors compared to healthy controls [59–61] and also patients with vascular risk factors but not ErectD [61]. This suggests that men with ErectD have impaired endothelium-dependent vasodilatation as well as smooth muscle dysfunction in the artery wall which supports the findings that ErectD predicts CVD.

Effect of phosphodiesterase type 5 (PDE5) inhibitors on EndoD and ErectD and CVD

Phosphodiesterase type 5 (PDE5) inhibitors have been investigated for treatment and possible prevention of some cardiovascular conditions, specifically through the improvement in EndoD [64,65]. Phosphodiesterases type 5 catalyze the degradation of cGMP, and are metabolized by PDE5 inhibitors. PDE5 is the isoform generally expressed in the penile corpus cavernosum however it is also found in other areas of the body including the pulmonary and systemic vasculature. In this context PDE5 inhibitors specifically prevent the breakdown of cGMP in the penis, thereby promoting vascular smooth muscle relaxation, arterial dilatation and venous constriction which results in an erection [66]. Therefore PDE5 inhibitors have been marketed as first line oral pharmacotherapy for men with ErectD, even though they were originally developed as an angina treatment [64]. Since PDE5 is also present in the vascular smooth muscle of the lung these inhibitors have also been used for treatment of pulmonary hypertension as well as other diseases [67]. Decreased EndoD is therefore a potential mechanism in which PDE5 inhibitors can improve cardiovascular conditions.

PDE5 inhibitor use has the potential to benefit several cardiovascular disease categories such as pulmonary hypertension, coronary artery disease and heart failure [68,69]. A prospective study showed PDE5 inhibitor use protected against incident cardiovascular events in men with diabetes and coronary artery disease [70]. Although the authors did acknowledge reduction of EndoD as a potential cause for the finding, this was not directly measured. Studies examining the effects of PDE5 inhibitors directly on EndoD have repeatedly shown significant improvements in several different populations [68]. It has been stated that although PDE5 inhibitors do show potential value in the treatment and protection against CVD this should only be secondary to reducing traditional risk factors [71]. Despite the value of PDE5 inhibitors in term of endothelial health, their long-term safety is an ongoing concern as they are a relatively new drug.

Population-based studies of ErectD in OSA

Although the association between ErectD and OSA has been recognized for over three decades [72], population-based studies

showing the joint prevalence of OSA and ErectD in the community using gold standard methods assessing OSA by overnight attended in-laboratory polysomnography (PSG) and erectile function by the IIEF questionnaire [38], are not available. Several other validated ErectD instruments have been applied in the research setting, including objective measurements of sleep related erections, as well as a variety of subjective questionnaires [39–46]. The only community based study to use a well-validated assessment of ErectD [73] and PSG found men with OSA were at two times greater risk of having ErectD [35] however did not report a joint prevalence of the two conditions. Other community based studies have reported inconsistent results which have been due to the reduced sensitivity of the subjective questionnaires which have been used to assess sleep disordered breathing rather than PSG [74,75]: Table 1.

Case-controlled and clinic-based studies of ErectD in OSA

In contrast to population-based studies, clinic-based studies using gold standard methods (IIEF and PSG), have found 40–70% of men who attended a sleep disorders clinic also had ErectD: Table 2. These data are consistent with the joint prevalence rates of 30–70% reported in other studies using PSG with other validated measures of ErectD: Table 2. In contrast to sleep clinic populations, there are no studies using both gold standard methods that have examined the proportion of men presenting for ErectD investigations with OSA: Table 3. However, studies using PSG do exist, in conjunction with NPT monitoring. The largest study ($n = 1025$) reported that 44% of men presenting with self-reported ErectD for further investigation also had OSA [76]. Similarly, two smaller studies ($n < 40$) have reported comparable prevalence rates in these clinic populations [77,78]. Studies have reported that OSA severity, particularly parameters measuring hypoxia, predicts the presence of ErectD [18,19,79–81]. One study showed in multivariate analysis that the mean nocturnal oxygen saturation was independently associated with ErectD [18]. Although common risk factors, including increasing age, past prostate surgery and vascular disease, also predicted ErectD, mean nocturnal oxygen maintained significance in the final adjusted model. This suggests that despite many common risk factors, intermittent hypoxia is a key underlying mechanism of the association between OSA and ErectD and points to a possible causal relationship however this cannot be deducted from these studies. Several studies have not shown an association between OSA severity and ErectD however this was using the apnea hypopnea index (AHI) as the severity parameter and even though this measure somewhat represents intermittent

Table 2
Prevalence of ErectD in a sleep clinic population.

First author	*N*	OSA definition (events/h)	Age (y)	ErectD measure	OSA measure	Joint prevalence (%)	Comments
Budweiser (2009) [18]	401	AHI > 5 ($n = 369$) AHI < 5 (controls, $n = 32$)	62 (54, 70) (ErectD) 50 (42, 55) (No ErectD)	IIEF-15	PSG	69	34% of controls had ErectD. Different to OSA group**. Erectile function decreased with worsening quartiles of AHI**, $MinSaO_2^{**}$ and $meanSaO_2^{**}$. MVA: $meanSaO_2^{**}$ predicted erectile function after adjustment for other risk factors.
Cruz (2012) [94]	98	AHI > 20	55 ± 11	Single question	Limited channel PSG	26	
Fanfulla (2000) [119]	25	AHI > 10	48 ± 12	Self-reported	PSG	72	
Goncalves (2005) [80]	98	AHI > 10	47 ± 10	Sexologist Interview	PSG	29	MVA: $MinSaO_2$* and age* not AHI, BMI or SaO_2 predicted ErectD. Sub-group analysis: $MinSaO_2$ >80%: 15% with ErectD $MinSaO_2$ ≤80%: 40% with ErectD. Different between groups**.
Guilleminault (1977) [72]	25	NR	44 (25–65)	Self-reported impotence	PSG	48	Impotence defined as ErectD and/or reduced sexual drive.
Guilleminault (1981) [120]	49	NR	47 (12–66)	Self-reported	PSG	NR	44% had erectile or ejaculatory difficulties
Hoekema (2007) [103]	96	AHI > 5 ($n = 48$) ND (controls, $n = 48$)	49 ± 9 48 ± 8	GRISS	PSG	NR	More ErectD* in OSA than controls.
Margel (2004) [79]	209	AHI 5–20 ($n = 80$) AHI 20–40 ($n = 60$) AHI > 40 ($n = 46$) AHI < 5 (controls, $n = 23$)	44 ± 12 44 ± 12 50 ± 10 50 ± 8	IIEF-5	PSG	NR	All aspects of erectile function declined with increased OSA severity*. Severe OSA (AHI > 40) had increased ErectD compared to all other groups*. Those with severe ErectD had the greatest AHI.
Petersen (2010) [82]	308 1185	AHI > 5 ND (controls, collected separately)	51 ± 10	BMSFI LiSat	PSG	NR	BMSFI and LiSat outcomes worse in OSA compared to controls. AHI not associated with any outcomes.
Shin (2008) [19]	59	AHI > 10 ($n = 32$) AHI < 10 (controls, $n = 27$)	45 ± 10 43 ± 10	IIEF-5	PSG	59	30% of controls had ErectD. Different to OSA group*. ErectD correlated with $MinSaO_2$ ($r = 0.34$**) but not AHI ($r = 0.06$ NS).
Stannek (2009) [83]	186	AHI > 5 ($n = 131$) AHI < 5 (controls, $n = 55$)	51 ± 11	Single question from IIEF	PSG	NR	More ErectD in OSA than controls* AHI not associated with ErectD.
Zhuravlev (2009) [121]	72	NR	44 (32–56)	IIEF-5 NPT	PSG	44	

Data are mean ± standard deviation, mean (range) or median (25th, 75th percentiles). *$p < 0.05$, **$p < 0.01$.
AHI = apnea hypopnea index, BMI = body mass index, BMSFI = brief male sexual functioning inventory, ErectD = erectile dysfunction, GRISS = Golombok Rust inventory of sexual function questionnaire, IIEF = international index of erectile function, LiSat = Fugl-Meyer life satisfaction checklist, $MinSaO_2$ = minimum desaturation level, MVA = multi-variate analysis, ND = not done, NPT = nocturnal penile tumescence, NR = not reported, OSA = obstructive sleep apnea, PSG = polysomnography, RDI = respiratory disturbance index, SaO_2 = blood oxygen saturation, TST = total sleep time.

Table 3
Prevalence of OSA in an ErectD population.

First author	*N*	Study population	Age (y)	ErectD measure	OSA definition (events/h)	OSA measure	Joint prevalence (%)	Comments
Chediak (1996) [78]	37	NPT clinic	52 ± 14	NPT	AHI > 10	PSG	49	PSG confirmed on two nights
Foreman (1986) [122]	30	NPT clinic	NR	NPT	NR	Limited PSG	17	
Hirshkowitz (1990) [76]	1025	NPT clinic	54 (NR)	NPT	Apnea Index ≥ 5	PSG	44	
Pressman (1986) [77]	31	NPT clinic	58 ± 6.8	NPT	AHI ≥ 5	PSG	32	
Seftel (2002) [123]	285	Urology surgeons clinic	53 ± 13	Self-reported	NR	Cleveland sleep habits questionnaire	28 (at high risk of OSA)	63% had ErectD (n = 168)

Data are mean ± standard deviation.
AHI = apnea hypopnea index, ErectD = erectile dysfunction, ESS = Epworth sleepiness scale, IIEF = international index of erectile function, NPT = nocturnal penile tumescence, OSA = obstructive sleep apnea, PSG = polysomnography.

hypoxia it may be less sensitive [82,83]. Interestingly, excessive daytime sleepiness may also be predictive of ErectD. A study of men attending a sleep clinic found 80% of those who reported excessive sleepiness (Epworth sleepiness scale >10) were diagnosed with ErectD compared to only 20% of those without sleepiness [84]. Excessive sleepiness however may be a marker of many conditions associated with ErectD including obesity and therefore is an unreliable marker of OSA.

As previously discussed, EndoD has been proposed as the underlying cause of ErectD (Fig. 1). OSA has been causatively linked with EndoD through a number of mechanistic pathways and thus it is conceivable that OSA would in turn lead to ErectD. On the other hand OSA has been proposed as a direct potential causal factor for ErectD through apnea-related disruption of REM sleep. During REM related nocturnal penile tumescence [20] the penile blood engorgement is thought to increase corporeal oxygenation and protect the morphological integrity of the penis [20,85]. Although it is conceivable that some ErectD in OSA is directly caused by REM sleep disturbance, we would argue that the majority would result from the promotion of EndoD (discussed further on).

Overall, the evidence shows an increased joint prevalence of ErectD and OSA despite several limitations including studies being conducted in varying and/or small populations and the use of different outcome measurement tools: Tables 1–3.

Treatment studies of ErectD in OSA

As there are currently no longitudinal studies in the literature regarding the relationship between the development of OSA and

Table 4
CPAP treatment and erectile dysfunction.

First author	*N*	Age (y)	AHI (events/h)	Duration	Erectile function measure	Change in erectile function with CPAP	Comments
Randomized controlled studies							
Li (2004) [87]	27 CPAP (n = 15) Control (n = 12)	NR	45 ± 11 42 ± 14	1 mo	IIEF-5	↑* compared to controls (non-English text)	
Observational studies							
Cruz (2012) [94]	98	55 ± 11	52.2 ± 21.4	6 mo	Likert scale	12%↑ (NS from baseline) 5%↓ (NS from baseline)	
Goncalves (2005) [80]	17	48 ± 9	71.4 ± 26.8	1 mo	Sexologist Interview	ErectD resolved in 76%* (13 out of 17 patients).	OSA parameters did not predict ErectD change
Karacan and Karatas (1995) [88]	22	54 (27–73)	49.2 ± 28	1 night	NPT	33% ↑ abnormal NPT	
Karkoulias (2007) [89]	15	56 ± 4	7.3 ± 1.2	3 mo	IIEF SIA	↑*	
Margel (2005) [92]	60	54 ± 10 (↔) 54 ± 11 (↑) 59 ± 10 (↓)	40.6 ± 18.1 (↔) 53.7 ± 15.2 (↑) 38.4 ± 18.9 (↓)	17 mo (range 12–26)	IIEF-5	20% ↑ (**from baseline) 18% ↓ (**from baseline)	UCA: ΔIIEF vs Baseline $MinSaO_2$ (r = −0.37**), CPAP adherence (r = 0.69*). ΔIIEF not correlated with RDI (NS).
Perimenis (2007) [93]	48 COPD + OSA	53 ± 10	28.3 ± 23.2	6 mo	ErectD Intensity Score	↑**	AHI greater in patients who ↑**. ΔIIEF positively correlated with age, AHI.
Petersen (2012) [91]	146	52 ± 10	43.3 ± 26.3	12 mo	BMSFI	↑*	

↑ denotes an improvement, ↓denotes a worsening, ↔ denotes not change. Data are mean ± standard deviation or mean (range). *$p < 0.05$, **$p < 0.01$.
AHI = apnea hypopnea index, CPAP = continuous positive airway pressure, BMSFI = brief male sexual functioning questionnaire, COPD = chronic obstructive pulmonary disease, ErectD = erectile dysfunction, EF = erectile function, IIEF = international index of erectile function, IIEF-5 = 5-item international index of erectile function, GRISS = Golombok Rust inventory of sexual function, LiSat11 = Life satisfaction 11, MAS = mandibular advancement splint, $MinSaO_2$ = minimum desaturation level, NPT = nocturnal penile tumescence, OSA = obstructive sleep apnea, RDI = respiratory disturbance index, SIA = successful intercourse attempts, UCA = univariate correlational analysis.

Table 5
Studies of CPAP with comparator arm.

First author	*N*	Age (y)	AHI (events/h)	Duration, design	Erectile function measure	Erectile function changes	Comments
Randomized controlled studies							
Hoekema (2007) [66]	48 CPAP ($n = 27$) MAS ($n = 21$)	51 ± 9 48 ± 8	46.7 (10–64.4) 20.6 (9.5–31.1)	2–3 mo, parallel	GRISS	↔CPAP, ↔MAS. Between-group NR.	
Perimenis (2004) [96]	30 CPAP ($n = 15$) Sildenafil ($n = 15$)	56 ± 4 56 ± 6	7.3 ± 1.2 7.4 ± 1.4	3 mo, parallel	IIEF-5 SIA	↑ (NR) Sildenafil, ↑CPAP (NR) but Sildenafil was superior**.	
Perimenis (2007) [98]	40 CPAP ($n = 20$) CPAP + Sildenafil ($n = 20$)	56 ± 5	15.1 ± 3.9	6 wk, CO	ND SIA		SIA greater with Sildenafil that CPAP**.
Perimenis (2007) [97]	40 CPAP ($n = 20$) Sildenafil ($n = 20$)	56 (48–62) 55 (42–64)	8.9 (6–25) 9.9 (6–24)	12 wk, parallel	IIEF SIA	↑** CPAP, ↑** Sildenafil but Sildenafil was superior*	SIA greater with Sildenafil that CPAP**.
Taskin (2010) [100]	40 CPAP ($n = 20$) Anti-Depressant ($n = 20$)	51 ± 7 53 ± 7	35 ± 19.3 33 ± 21.7	1 mo, parallel	IIEF-5	↑** CPAP, ↔ (NS) anti-depressant	Stratifying by $MinSaO_2$ (80%) did not show correlation with ΔIIEF.
Observational studies							
Budweiser (2013) [95]	91 CPAP users (any use, $n = 56$) Non-CPAP users ($n = 35$)	55 (48, 62) 58 (45, 69)	28.1 (18.0, 40.0) 14.7 (6.8, 23.7)	3 y	IIEF-15	↔CPAP users, ↓ non-users. Between-group NS. Sub-analysis: 1): No difference in those with moderate/severe ErectD. 2): CPAP↑* compared to non-users in those with both moderate-severe ErectD and mean nocturnal SaO_2 <93%.	61.5% had ErectD
Ceylan (2013) [124]	23 CPAP ($n = 16$) Surgery ($n = 7$)	46 ± 11	48.8 ± 32.5	3 mo	IIEF-5	↑*	Results combined for both treatments
Khafagy (2012) [102]	80 CPAP ($n = 57$) Surgery ($n = 23$)	42 ± 9	33.4 ± 1.7 37.0 ± 7.6	3 mo	NPT + IIEF-5	↑** ErectD resolved in 22.5% (IIEF-5) ↑* Percentage rigidity (NPT)	Results combined for both treatments Commonly reported NPT parameters not reported.
Shin (2013) [101]	56 UPPP ($n = 30$) CPAP ($n = 16$) MAS ($n = 10$)	44 ± 10 53 ± 8 49 ± 9	29.6 ± 21.6 51.6 ± 17.1 29.3 ± 10.6	7 (4, 15) mo	IIEF-5	↑UPPP (*from baseline) ↔CPAP (NS) ↔MAS (NS)	No comparisons between groups

↑ denotes an improvement, ↔ denotes no change. Data are mean ± standard deviation, mean (range) or median (25th, 75th percentile). *$p < 0.05$, **$p < 0.01$. AHI = apnea hypopnea index, CO = cross-over, CPAP = continuous positive airway pressure, ErectD = erectile dysfunction, IIEF = international index of erectile function, IIEF-15 = 15-item international index of erectile function, IIEF-5 = 5-item international index of erectile function, GRISS = Golombok Rust inventory of sexual function, MAS = mandibular advancement splint, $MinSaO_2$ = minimum desaturation level, ND = not done, NPT = nocturnal penile tumescence, NR = not reported, SaO_2 = oxygen saturation levels, SIA = successful intercourse attempts, UPPP = uvulopalatopharyngoplasty.

ErectD, direction of causality is yet to be determined. OSA treatment studies should help answer this question, however to date, most interventional studies have failed to definitively support OSA as a causal factor in ErectD.

Although a recent review concluded that CPAP improves ErectD in men with both erectile dysfunction and OSA, it was based on theoretical mechanisms combined with observational and uncontrolled clinical studies [20]. Importantly, a pivotal randomized sham-controlled study showing that CPAP improves ErectD has yet to be performed. Sham-control is essential, because the primary outcome of therapy is self-reported [86], but none of the available studies are sham-controlled: see Table 4. The only randomized no-treatment controlled study (comparing CPAP with a non-treated control group) showed a significant improvement in ErectD after 1 mo of CPAP in 27 men [87], but considerable residual disease persisted even in those randomized to CPAP therapy and the duration of therapy was relatively short.

Within-individual, before and after studies are also presented in Table 4. Improvements in sexual function have been reported after 1–3 mo of CPAP treatment [80,88–91]. Longer term (6–12 mo) uncontrolled studies also show maintenance of these improvements with continued CPAP treatment at least in those with severe disease [92,93]. Another study found one in three men had resolution of their ErectD after 6 mo of CPAP use but the percent of men with ErectD at 6 mo (17%) was not significantly different from that at baseline (25%) [94]. One longer term (3 y) observational study ($n = 91$) found that in men with OSA and poor sexual function, overall satisfaction and sexual desire was better in those who chose to use CPAP ($n = 56$) compared to non-CPAP users ($n = 35$). This was due to CPAP preventing a decline in sexual function that occurred in non-CPAP users. A similar trend was seen for erectile function but the difference did not reach significance. In those men who had moderate-severe ErectD, between group differences were seen in overall sexual function, orgasmic function, sexual desire and overall satisfaction but not

erectile function. In contrast, erectile function improved only in men with both moderate-severe ErectD and low nocturnal oxygen saturation levels [95]. This suggests that those with intermittent hypoxia have greater response to treatment most likely because they have greater impairment to begin with.

Other randomized comparison studies have also been conducted however they have not included control groups without treatment: Table 5. Studies comparing sildenafil (a PDE5 inhibitor) to CPAP [89,96,97] or sildenafil with CPAP [98] have shown significant improvements in the IIEF after 1–3 mo of CPAP treatment in men however adverse event information regarding the effects of sildenafil on OSA were not reported. PDE5 inhibitors have been previously shown to worsen sleep disordered breathing [99] and therefore their effect on OSA needs to be documented. Another study compared CPAP to an anti-depressant and showed the IIEF-5 to improve significantly after CPAP but not the anti-depressant, however the between-group difference was not reported [100]. In an observational study using either CPAP, mandibular advancement splint, or surgery (uvulopalatopharyngoplasty), as selected by the patient, only those who had surgery were found to have improvements in the IIEF, however despite surgery improving but not resolving OSA [101]. Similarly, a study showed both surgery (in people who were CPAP non-compliant) and CPAP in a separate group of men had an overall improvement in both subjective and objective (NPT) measurements of ErectD, however the improvements per treatment were not reported [102]. Finally a study comparing CPAP to mandibular advancement splint showed no changes in erectile function after either treatment but did not assess ErectD by IIEF, and did not exclude men without ErectD [103].

Effects of PDE5 inhibitors in OSA

As previously established ErectD is common in men with OSA and thus it is predicted that treatment with PDE5 inhibitors may be warranted in these men in order to restore erectile function. Furthermore as previously shown PDE5 inhibitors have the potential to reverse EndoD which may be beneficial in patients that refuse or cannot use CPAP, which has been estimated as high as 50% of users [104]. The safety of using PDE5 inhibitors in men with OSA has however been questioned [105]. PDE5 inhibitors reduce subjective and objective nasal patency which has led to the suggestion that their use may promote OSA in susceptible individuals by facilitating airway occlusion [106,107]. However in the only randomized controlled trial, despite an increase in subjective and objective nasal patency after the administration of a PDE5 inhibitor, between group comparisons between the placebo and active treatment were not reported [107]. The first safety study conducted in an OSA population was a randomized order placebo-controlled crossover trial. This study showed that a single mid-range 50 mg dose of sildenafil increased the AHI, desaturation index, and amount of time hypoxic in 13 men with severe OSA [99]. The same study also showed a worsening in the arousal index and heart rate variability in REM sleep [108]. However efficacy studies which have used PDE5 inhibitors in men with ErectD and OSA have not reported safety outcomes specifically in terms of sleep disordered parameters [96,98,109]. As OSA and ErectD commonly co-exist the safety of PDE5 inhibitors in these patients, does need to be explored further in larger groups with higher exposure. This is of importance as there is a high chance that men with untreated or undiagnosed OSA will be prescribed these drugs for erectile issues.

It is generally believed that EndoD is the underlying cause of ErectD and this is confirmed by clinical studies showing the two conditions occur together. Furthermore ErectD is an established risk factor for CVD most likely due to underlying EndoD. Therefore it is conceivable that EndoD promotes the manifestation of ErectD in OSA patients. EndoD is strongly associated with OSA and the increasing evidence from randomized controlled trials of CPAP suggest that OSA can cause EndoD (see below) strengthens this hypothesis.

EndoD and ErectD in OSA

Substantial evidence supports OSA as a causal factor in the promotion of EndoD. Most studies have concluded that OSA independently impairs endothelial function, although it is beyond the scope of this review to detail studies which support this [24,110] and the relationship is through a variety of mechanisms (Fig. 1) [23,111,112]. The strongest evidence comes from recent randomized controlled trials which have demonstrated reversal of EndoD with CPAP [113–116]. These randomized trials have specifically confirmed that CPAP improves endothelium-dependant vasodilatation. The improvement is most consistent for measures in larger conduit vessels which may have direct relevance to ErectD in this group (see below). The effects on endothelium-dependant vasodilatation of the smaller vessels as well as endothelium-independent vasodilatation requires the conduction of larger and possibly longer randomized controlled trials [116,117]. In addition, since approximately 50% of CPAP users do not use their machine adequately or stop using it completely [104] other treatments that can reverse EndoD should also be explored.

Hence overall, the current evidence supports independent associations between OSA and ErectD as well as between OSA and EndoD however the complex inter-relationships between all three conditions cannot be truly determined by the current literature. To our knowledge there are no current observational data from clinical or population studies nor interventional studies available which examine all three conditions simultaneously. Nevertheless, the data presented in this review provides a unifying hypothesis to explain how OSA may cause ErectD through worsening of EndoD. Studies recruiting men with both OSA and ErectD are a priority as these men could be at a heightened risk for future cardiovascular events. Controlled studies in this population should explore the effect of not only CPAP on both EndoD and ErectD but also the effect of PDE5 inhibitors on these outcomes while specifically examining OSA safety. There is potential for the use for PDE5 inhibitors in OSA to promote EndoD improvement as CPAP withdrawal rates are high. Furthermore, in a man with both OSA and Erect and therefore most likely EndoD, the use of CPAP plus a PDE5 inhibitor may provide a synergistic effect on ErectD and EndoD. Further studies are required to investigate these interactive effects.

Conclusion

There is substantial evidence that EndoD is a strong contender as the mechanism linking ErectD and OSA. Both erectile function and endothelial function are worsened in those with OSA, with growing evidence that both improve with CPAP. The use of PDE5 inhibitors can improve endothelial function; however they may have some detrimental effects in regard to OSA. Well-designed randomized controlled studies are needed to further solidify EndoD as the pathophysiological link between OSA and ErectD. Clinical application of this evidence is warranted, through screening of OSA and ErectD patients for the presence of the alternate condition, and identification of the increased cardiovascular risk for these patients.

Conflict of interests

None to declare.

Practice points

- Erectile dysfunction is common in obstructive sleep apnea, as is obstructive sleep apnea in erectile dysfunction. Despite a strong evidence of an association, direction of causality is yet to be determined as the two conditions have many common risk factors but observational and uncontrolled data suggest that obstructive sleep apnea is independently associated with erectile dysfunction.
- Obstructive sleep apnea is associated with the development of endothelial dysfunction. Endothelial dysfunction is an important underlying link between obstructive sleep apnea and erectile dysfunction and likely plays a key role in the increased cardiovascular morbidity and mortality associated with obstructive sleep apnea.
- PDE5 inhibitors potentially can reduce endothelial impairment however data regarding their long-term safety and use in obstructive sleep apnea is limited.

Research agenda

- Larger sham-controlled studies examining efficacy of continuous positive airway pressure on erectile dysfunction using gold standard validated tools for outcome measures are required to determine whether obstructive sleep apnea causes erectile dysfunction.
- Studies in men with both erectile dysfunction and obstructive sleep apnea should be a priority. Controlled studies in this population should explore the effect of not only continuous positive airway pressure on both endothelial dysfunction and erectile dysfunction but also the effect of PDE5 inhibitors on these outcomes while specifically examining obstructive sleep apnea safety. Furthermore whether there is a synergistic effect, such as a greater effect in endothelial dysfunction and erectile dysfunction in a man receiving both continuous positive airway pressure and a PDE5 inhibitor could also be investigated.

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